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A concise synthesis of meridianin F

Jonathan Sperry

School of Chemical Sciences, University of Auckland, 23 Symonds Street, Auckland, New Zealand

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ABSTRACT

A concise synthesis of the protein kinase inhibitor meridianin F has been achieved in good overall yield starting from 5,6-dibromoindole-3-carbaldehyde.

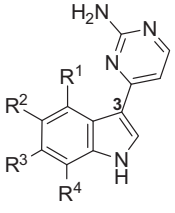
Meridianins A–G (**1**–**7**) are a family of alkaloids isolated from the south Atlantic tunicate *Aplidium meridianum*.[1] These natural products all possess a molecular architecture comprising an indole substituted at C3 with a 2-aminopyrimidine ring. Furthermore, the meridianins have been shown to display varying degrees of protein kinase inhibition, with some derivatives also demonstrating anti-tumour activity (Fig. 1).[1,2]

Due to the unique structure and potent biological activity of the meridianin family of natural products, synthetic studies have been readily forthcoming from several groups. Numerous syntheses of members of the family exist,[3,5] as well as syntheses of several analogues[4,5] that emphasize the importance of this class of compounds as potential leads in cancer chemotherapy.

Our laboratory has an ongoing interest in alkaloids bearing unusual halogenation patterns that have subsequently led to the first syntheses of several natural products possessing the rare 5,6-dibromoindole moiety.[6] The unusual bromination pattern was installed using an historic dibromination of an indole-3-carboxylate,[6] a result that was simultaneously reported by Grainger and co-workers.[7a] Until these reports, synthetic studies towards compounds possessing the 5,6-dibromoindole moiety were sparse and the desired materials were often only obtained as unwanted by-products. In a recent development, Mollica et al. have reported the first asymmetric route to a 5,6-dibromotryptophan derivative that relies on the selective monobromination of 6-bromoisatin followed by reduction to 5,6-dibromoindole,[7b] thus providing a valuable addition to current methods available for the synthesis of this heterocyclic moiety. Furthermore, the aforementioned report by Grainger and co-workers describing the first synthesis of meridianin F (**6**)[7a] prompts us to disclose our own efforts in this field.

Meridianin F (**6**) is the only member of the family to possess the rare 5,6-dibromoindole moiety, which appears to be partly responsible for its low micromolar inhibition of several protein kinases.[1b] For these reasons, and intrigued that meridianin F (**6**) is a minor component not originally detected in the extracts of *A. meridianum*,[1a,c] we decided to initiate the synthesis of meridianin F (**6**).

The retrosynthesis of meridianin F (**6**) is shown in Scheme 1. We planned to use the well-established Bredereck 2-aminopyrimidine synthesis[3b,8] between enaminone **8** and guanidine followed by N-debenzylation. The enaminone **8** was to be accessed by reac-



meridianin A (**1**) R^1 = OH, R^2 = R^3 = R^4 = H
meridianin B (**2**) R^1 = OH, R^2 = R^4 = H, R^3 = Br
meridianin C (**3**) R^1 = R^3 = R^4 = H, R^2 = Br
meridianin D (**4**) R^1 = R^2 = R^4 = H, R^3 = Br
meridianin E (**5**) R^1 = R^2 = R^3 = H, R^4 = Br

meridianin F (**6**) R^1 = R^4 = H, R^2 = R^3 = Br

meridianin G (**7**) R^1 = R^2 = R^3 = R^4 = H

Figure 1. Meridianins A–G.

E-mail address: j.sperry@auckland.ac.nz

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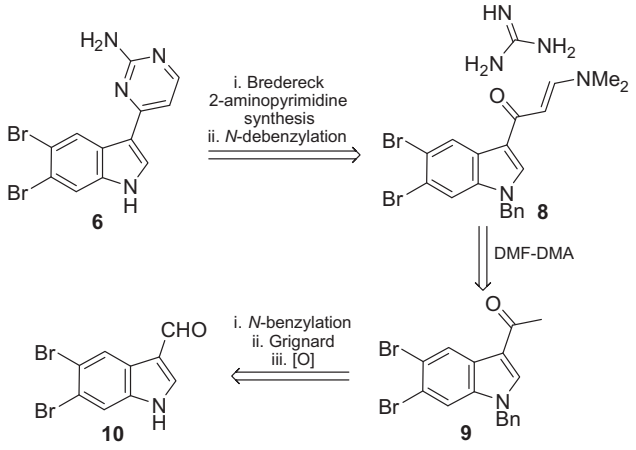
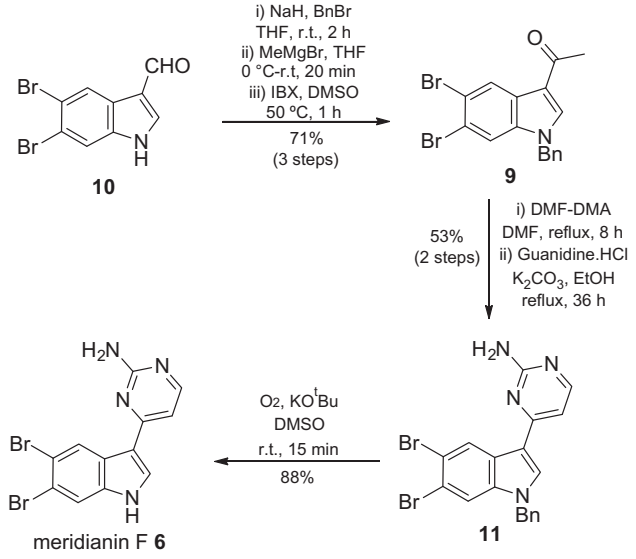


Scheme 1. Retrosynthesis of meridianin F.



Scheme 2. Synthesis of meridianin F.

tion of dimethylformamide dimethylacetal with the 3-acetylindole **9**, which in turn was envisioned to be readily available from 5,6-dibromo-3-carbaldehyde **10**[6] by N-benzylation followed by Grignard reaction and oxidation.

With multigram quantities of 5,6-dibromoindole-3-carbaldehyde **10** at hand,[6] straightforward benzylation, Grignard reaction with methylmagnesium bromide and oxidation with iodoxybenzoic acid (IBX) gave the key intermediate **9** in excellent yield over three steps (from **10**) which only involved a single purification operation. Next, 3-acetylindole **9** underwent smooth enaminone formation followed by immediate treatment with guanidine hydrochloride in the presence of potassium carbonate, gratifyingly affording *N*-benzyl meridianin F (**11**). Finally, the pivotal N-debenzylation was attempted. Somewhat unsurprisingly, various hydrogenation conditions resulted in a significant amount of debromination, a result noted previously when attempting hydrogenation on 5,6-dibromoindoles.[6] However, treatment of **11** with potassium *tert*-butoxide in DMSO under an atmosphere of oxygen[9] effected swift N-debenzylation, gratifyingly delivering meridianin F in excellent yield (Scheme 2). The spectroscopic data of synthetic meridianin F (**6**) were identical to those of the natural product.[1c,10]

In conclusion, we have completed a concise synthesis of the protein kinase inhibitor meridianin F, an alkaloid possessing the rare 5,6-dibromoindole moiety. The synthetic route proceeds in good overall yield and each step is readily scalable.

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Supplementary data

Supplementary data (experimental details for the preparation of meridianin F (**6**), along with relevant spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.073.

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